Genetic analysis of obstructive sleep apnoea discovers a strong association with cardiometabolic health

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Five OSA-associated loci were found, highlighting the causal link between obesity and OSA, and providing evidence for non-BMI-dependent effects. OSA comorbidities were correlated genetically for OSA, showing these diseases may have a shared genetic basis. https://bit.ly/36Rfq1Y

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ABSTRACT There is currently limited understanding of the genetic aetiology of obstructive sleep apnoea (OSA). We aimed to identify genetic loci associated with OSA risk, and to test if OSA and its comorbidities share a common genetic background.

We conducted the first large-scale genome-wide association study of OSA using the FinnGen study (217 955 individuals) with 16 761 OSA patients identified using nationwide health registries.

We estimated 0.08 (95% CI 0.06–0.11) heritability and identified five loci associated with OSA ($p<5.0\times10^{-8}$): rs4837016 near *GAPVD1* (GTPase activating protein and VPS9 domains 1), rs10928560 near *CXCR4* (C-X-C motif chemokine receptor type 4), rs185932673 near *CAMK1D* (calcium/calmodulin-dependent protein kinase ID) and rs9937053 near *FTO* (fat mass and obesity-associated protein; a variant previously associated with body mass index (BMI)). In a BMI-adjusted analysis, an association was observed for rs10507084 near *RMST*/*NEDD1* (rhabdomyosarcoma 2 associated transcript/NEDD1 γ-tubulin ring complex targeting factor). We found high genetic correlations between OSA and BMI (r_g=0.72 (95% CI 0.62–0.83)), and with comorbidities including hypertension, type 2 diabetes, coronary heart disease, stroke, depression, hypothyroidism, asthma and inflammatory rheumatic disease (r_g>0.30). The polygenic risk score for BMI showed 1.98-fold increased OSA risk between the highest and the lowest quintile, and Mendelian randomisation supported a causal relationship between BMI and OSA.

Our findings support the causal link between obesity and OSA, and the joint genetic basis between OSA and comorbidities.

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Data availability: The FinnGen individual-level data may be accessed through applications to the Finnish biobanks' FinnBB portal, Finngenious (www.finbb.fi). Summary data can be accessed through the FinnGen site www.finngen.fi/en/access_results. The full genotyping and imputation protocol for FinnGen is described at https://doi-org.libproxy.helsinki.fi/10.17504/protocols.io.nmndc5e

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Introduction

Obstructive sleep apnoea (OSA) is a severe sleep disorder affecting at least 9% of the population. Prevalence increases with higher age, reaching >35% in individuals >60 years of age [1]. Despite a recognised health impact, and available diagnostic tools and treatments, the condition remains underdiagnosed [2, 3]. OSA is characterised by repetitive episodes of nocturnal breathing cessation due to upper airway collapse resulting in mild to severe sleep deprivation and dysregulation of sleep, breathing and blood pressure. These conditions may lead to serious comorbidities through intermittent hypoxia, systemic inflammation and sympathetic activation [4]. Furthermore, OSA is influenced by multiple risk factors such as obesity, male sex, family history of OSA, high age and problems of upper airway flow or jaw anatomy [5].

Consequently, OSA is a serious public health problem due to its many cardiometabolic comorbidities, including an increased risk for coronary heart disease (CHD), type 2 diabetes (T2D) and its complications, and ultimately increased mortality [6, 7]. In addition, comorbidities such as depression, hypothyroidism, asthma and inflammatory rheumatic disease (IRD) are linked with OSA [8–11]. IRD might manifest as a comorbidity of OSA through effects on the temporomandibular joint, which rotates the lower jaw backward causing narrowing of the upper airway [12].

Genetic studies provide a tool to identify independent genetic risk factors that modulate disease risk and to examine causal pathways between comorbidity traits. Genome-wide association studies (GWASs) in OSA patients have previously identified associations with OSA severity measured using the apnoea–hypopnoea index (AHI) or respiratory event duration. The genome-wide significant findings from these studies and the corresponding associations from our previous study are shown in supplementary table S1 [13–15]. Larger-scale GWASs have been performed on OSA-related phenotypes such as snoring [16]. However, knowledge about OSA predisposing genetic loci is thus far limited [17].

To test genetic associations with OSA we utilised the FinnGen study with genetic profiling for 217 955 individuals and OSA diagnosis based on International Statistical Classification of Diseases and Related Health Problems, Ninth (ICD-9) and Tenth (ICD-10) Revision codes obtained from the Finnish National Hospital Discharge Registry and the Causes of Death Registry. The registries have excellent validity and coverage [18]. Combining the OSA diagnosis (ICD-10: G47.3; ICD-9: 3472A) and related risk factors and comorbidities with the genotyping data allows identification of risk variants, helps elucidate biological disease mechanisms and enables evaluation of OSA-related disease burden on a population level.

The aim of the study is to identify genetic loci associated with OSA risk, and to test if OSA and its comorbidities share a common genetic background. While there are previous small-scale GWASs on OSA severity, to the best of our knowledge this is the first large-scale GWAS on the risk of OSA.

Materials and methods

General information

We selected into further analyses those comorbidities which have previously been shown to associate with OSA in epidemiological studies, including obesity, hypertension, T2D, CHD, stroke, depression, hypothyroidism, asthma and IRD [8–12, 19–22].

Variant positions are reported in Genome Reference Consortium Human genome build 38 coordinates (GRChb38). All effect sizes and allele frequencies are reported in terms of the alternate allele.

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Study sample in FinnGen

FinnGen (www.finngen.fi/en) is a large biobank study that aims to genotype 500 000 Finns, including prospective and retrospective epidemiological and disease-based cohorts as well as hospital biobank samples (supplementary table S2). FinnGen combines this data with longitudinal registry data that record healthcare events over the entire lifespan, including the National Hospital Discharge Registry (available from 1968), Causes of Death Registry (available from 1969), Cancer Registry (available from 1953) and Medication Reimbursement Registry (available from 1995), all these using unique national personal identification codes. Registry data were available from the beginning of the registry until December 31, 2018 (supplementary figure S1). The data consist of 218 792 censored individuals until spring of 2020. FinnGen's genotyping and imputation protocols are described in the supplementary material.

To examine OSA patients more specifically, 837 individuals who had ICD-10: G47 (Sleep disorders) were excluded from the controls and thus the remaining sample size was 217 955 participants. Of them, 16 761 (7.7%) had an OSA diagnosis and 10 557 (63.0%) of OSA patients were male. Baseline characteristics and OSA comorbidities of the participants are presented in table 1. Differences in baseline demographics and clinical characteristics were tested using a logistic regression model. The model was adjusted for sex, age and the 10 first principal components (PCs); the model for age was adjusted for sex and the 10 first PCs and the model for sex was adjusted for age and the 10 first PCs.

The diagnosis of OSA was based on ICD codes (ICD-10: G47.3; ICD-9: 3472A), which were obtained from the Finnish National Hospital Discharge Registry and the Causes of Death Registry. This diagnosis is based on subjective symptoms, clinical examination and sleep registration applying AHI $\geqslant$5 events·h^{-1} or respiratory event index $\geqslant$5 events·h^{-1}. By combining ICD codes from different registries, we generated disease end-points. Supplementary table S3 describes how end-points were constructed for each phenotype.

All prescription medicine purchases were retrieved from the Social Insurance Institution of Finland (KELA) registry for prescription drug purchases (available from 1995; excluding over-the-counter medicines and medication administered at hospitals). The drugs are coded by the Anatomical Therapeutic Chemical Classification System (supplementary figure S1).

Study samples in other cohorts

The UK Biobank (UKBB; www.ukbiobank.ac.uk) is a major national and international health resource, with the aim of improving the prevention, diagnosis and treatment of a wide range of serious and life-threatening illnesses. UKBB recruited 500 000 people during 2006–2010 from across the UK. OSA diagnosis was based on ICD-10: G47.3. The UKBB study sample included 4471 OSA cases and 403 723 controls.

TABLE 1 Baseline characteristics and previously known obstructive sleep apnoea (OSA) comorbidities between OSA and non-OSA individuals in the FinnGen cohort

	All	Non-OSA	OSA	OR (95% CI)	p-value
Subjects	217 955	201 194	16 761		
Sex					
Male	94 799 (43.5)	84 242 (41.9)	10 557 (63.0)	2.26 (2.19–2.34)	$<2.00\times10^{-16}$
Female	123 156 (56.5)	116 952 (58.1)	6204 (37.0)		
Age years	52.4±17.5	51.8±17.7	58.9±13.3	1.02 (1.02–1.03)	$<2.00\times10^{-16}$
Age at OSA diagnosis years			55.3±11.9		
BMI kg·m^{-2}	27.25±5.34	26.87±5.02	31.72±6.74	1.15 (1.15–1.16)	$<2.00\times10^{-16}$
Comorbidity					
Hypertension	55 678 (25.5)	47 549 (23.6)	8129 (48.5)	2.44 (2.36–2.53)	$<2.00\times10^{-16}$
T2D	29 054 (13.3)	23 932 (11.9)	5122 (30.6)	2.60 (2.50–2.70)	$<2.00\times10^{-16}$
CHD	20 925 (9.6)	18 495 (9.2)	2430 (14.5)	1.11 (1.06–1.17)	1.04×10^{-5}
Stroke	11 671 (5.4)	10 414 (5.2)	1257 (7.5)	1.10 (1.03–1.17)	3.29×10^{-3}
Depression	23 160 (10.6)	20 094 (10.0)	3066 (18.3)	2.56 (2.45–2.67)	$<2.00\times10^{-16}$
Hypothyroidism	26 228 (12.0)	23 384 (11.6)	2844 (17.0)	1.85 (1.77–1.94)	$<2.00\times10^{-16}$
Asthma	20 520 (9.4)	17 358 (8.6)	3162 (18.9)	2.58 (2.47–2.69)	$<2.00\times10^{-16}$
IRD	12 961 (5.9)	11 555 (5.7)	1406 (8.4)	1.48 (1.39–1.57)	$<2.00\times10^{-16}$

Data are presented as n, n (%) or mean±SD, unless otherwise stated. BMI: body mass index; T2D: type 2 diabetes; CHD: coronary heart disease; IRD: inflammatory rheumatic disease. Age and BMI were measured at the time when the biobank sample was given. BMI was measured in 159 731 individuals, including 12 759 OSA cases and 146 972 controls.

The Estonian Biobank is a population-based biobank of the Estonian Genome Center at the University of Tartu (EGCUT; www.biobank.ee). The cohort size is currently close to 150 000 participants. Patients were selected by ICD-10: G47.3. For additional conformation of the diagnosis, treatment service codes from the Health Insurance Fund were also used. The EGCUT study sample included 4930 OSA patients and 61 056 controls.

All New Diabetics in Scania (ANDIS; www.andis.ludc.med.lu.se) aims to recruit all incident cases of diabetes within Scania County in Southern Sweden. All healthcare providers in the region were invited; the current registration covered 14 625 patients. OSA was defined by ICD-10: G47.3. The ANDIS study sample included 947 OSA patients and 9829 controls.

Validation of OSA diagnosis

For validation of OSA diagnosis, we collected 1000 OSA patients treated in the Hospital District of Helsinki and Uusimaa (HUS) during 2008–2011 and 2016–2019 using the diagnoses derived from HUS's Hospital Discharge Registry and the individual-level medical records.

The diagnosis for OSA was confirmed using the International Classification Criteria for Sleep Disorders, which requires either signs/symptoms (*e.g.* associated sleepiness, fatigue, insomnia, snoring, subjective nocturnal respiratory disturbance or observed apnoea) or associated medical or psychiatric disorder (*i.e.* hypertension, coronary artery disease, atrial fibrillation, congestive heart failure, stroke, diabetes, cognitive dysfunction or mood disorder) coupled with five or more predominantly obstructive respiratory events per hour. Alternatively, a frequency of obstructive respiratory events of 15 h^{-1} satisfies the criteria, even in the absence of associated symptoms or disorders [23].

Genome-wide association testing

218 792 samples from FinnGen Data Freeze 5 with 2925 disease end-points were analysed using SAIGE (Scalable and Accurate Implementation of GEneralised mixed model), which uses the saddlepoint approximation to calibrate unbalanced case–control ratios [24]. Analyses were adjusted for current age or age at death, sex, genotyping chip, genetic relationship and the first 10 PCs. For OSA, we performed a GWAS in a similar manner (n=217 955, including 16 761 OSA patients and 201 194 controls), but adjusting also for body mass index (BMI) (n=159 731, including 12 759 OSA patients and 146 972 controls).

For replication of the FinnGen OSA GWAS results, we merged the evidence from the UKBB, EGCUT and ANDIS cohorts. The results were combined using inverse variance weighted fixed-effect meta-analysis using β estimates and β standard errors in the Metagen R package as implemented in R version 4.0.2 (www.r-project.org). The merged data consisted of 10 348 OSA cases and 474 608 controls.

The GWAS using UKBB data was calculated using SAIGE [24]. This subset included 4471 OSA cases and 403 723 controls, and was adjusted for birth year, sex, genetic relatedness and the first four PCs. In EGCUT, the data were analysed using SAIGE, and the model was adjusted for current age or age at death, sex, genetic relatedness and the first 10 PCs. The analysis included 4930 OSA patients and 61 056 controls. In ANDIS, the GWAS was calculated using the logistic regression model, which was adjusted for current age or age at death, sex and the first 10 PCs. The analysis included 947 cases and 9829 controls.

Linkage disequilibrium score regression

We used LDSC software to estimate single nucleotide polymorphism (SNP)-based heritability, genetic correlation and tissue-specific SNP heritability [25]. LDSC uses the linkage disequilibrium score regression method, which quantifies the contribution of each variant by examining the relationship between test statistics and linkage disequilibrium. In calculations we used linkage disequilibrium scores calculated from the European ancestry subset of the 1000 Genomes dataset [26]. To restrict the calculation to a set of common, well-imputed variants, we retained only those SNPs in the HapMap 3 reference panel [27].

To study genetic correlations between OSA, BMI, hypertension, T2D, CHD, stroke, depression, hypothyroidism, asthma and IRD, we used summary statistics from the FinnGen data. For sleep traits, we used summary statistics derived from the UKBB data. Study subjects self-reported snoring, sleep duration, sleepiness and chronotype [16, 28, 29]. Sleep efficiency (sleep duration divided by the time between the start and end of the first and last nocturnal inactivity period, respectively) was based on accelerometer-derived measures [30]. For tissue-specific SNP heritability, we used a method that combined data from the Encyclopedia of DNA Elements (ENCODE; www.encodeproject.org) and Genotype-Tissue Expression (GTEx; www.gtexportal.org/home) resources [31, 32].

Polygenic risk score and Mendelian randomisation

The polygenic risk score (PRS) for BMI was calculated using summary statistics for 996 250 variants [33]. The posterior effect sizes were calculated using the PRS-continuous shrinkage method (PRS-CS) [34]. PRS for OSA replication was calculated using dosage-weighted β estimates for each lead variant ($p<5\times10^{-8}$; n=5 variants). The scores were generated using Plink2 (www.cog-genomics.org/plink/2.0) in the FinnGen data and the weights from FinnGen were projected to the UKBB individual-level data.

We performed Mendelian randomisation analysis to investigate the causality between BMI and OSA using independent BMI SNPs [33]. A genetic variant associated with the exposure of interest (genetic instrument) was used to test the causal relationship with the exposure (BMI) and outcome (OSA) [35].

Gene-based analysis

Gene-based tests were performed using MAGMA (Multi-marker Analysis of GenoMic Annotation) as implemented on the Functional Mapping and Annotation (FUMA) platform, which provides aggregate association p-values based on all variants located within a gene and its regulatory region using information from 18 biological data repositories and tools [36]. This analysis includes a gene-based test to detect significant SNPs associated with OSA using FinnGen OSA summary statistics.

Results

OSA diagnosis shows excellent validity

We validated the OSA diagnosis using HUS's Hospital Discharge Registry, collecting information of 1000 patients and compared the registry data with the patients' medical records. OSA diagnosis has a validity showing >98% positive predictive value (supplementary figure S2).

OSA correlates strongly with cardiovascular and metabolic traits

To estimate strengths of associations between OSA and comorbidities, we utilised data from 217 955 individuals who participated in the FinnGen project. 16 761 (7.7%) had an OSA diagnosis and 10 557 (63%) of cases were male. The diagnoses were derived from ICD codes in the Finnish National Hospital Discharge Registry and from the Causes of Death Registry. Baseline characteristics of the FinnGen participants and odds for OSA-associated comorbidities are presented in table 1. Two-thirds (66.2%) of patients had BMI $\geqslant$25 kg·m^{-2}, as suggested by previous epidemiological reports [37].

GWAS of OSA reveals BMI-dependent and -independent associations

We estimated the heritability for OSA in FinnGen to be 0.08 (95% CI 0.06–0.11) before and 0.06 (95% CI 0.04–0.08) after adjusting for BMI. In a genome-wide association test, five distinct genetic loci were associated with OSA ($p<5.0\times10^{-8}$), as outlined in table 2, figure 1a and supplementary figure S3a, and with regional associations in supplementary figure S4. The lead variant in a locus on chromosome 16 was rs9937053, an intronic variant near *FTO* (fat mass and obesity-associated protein), $p=4.3\times10^{-16}$. In chromosome 12, the lead variant was rs10507084 near *RMST*/*NEDD1* (rhabdomyosarcoma 2 associated transcript/NEDD1 γ-tubulin ring complex targeting factor), $p=2.8\times10^{-11}$, where *RMST*, a long noncoding RNA, was the nearest gene and *NEDD1* was the nearest protein coding gene. On chromosome 10, the lead variant was rs185932673, an intronic variant near *CAMK1D* (calcium/calmodulin-dependent protein kinase ID), $p=2.4\times10^{-8}$. In chromosome 9, the lead variant was rs4837016 near *GAPVD1* (GTPase activating protein and VPS9 domains 1), $p=1.5\times10^{-8}$. In chromosome 2, the lead variant rs10928560 was near *CXCR4* (C-X-C motif chemokine receptor 4), $p=2.8\times10^{-8}$. Four out of five of these OSA-associated lead variants have also been previously associated with BMI ($p<0.01$) [38–40], with the exception of rs10507084 at the *RMST/NEDD1* locus. Conditional analyses of the associated loci did not suggest any additional associations. Adjusting for BMI did not affect the association for variant rs10507084 ($OR_{unadjusted}$ 1.11 (95% CI 1.08–1.15); $p=2.8\times10^{-11}$ *versus* $OR_{BMI\text{-}adjusted}$ 1.12 (95% CI 1.08–1.17); $p=9.7\times10^{-10}$) (table 2, figure 1b, and supplementary figures S3b and S4), suggesting BMI-independent mechanisms for rs10507084 in OSA predisposition. As a sensitivity analysis we conducted a GWAS where individuals with snoring (ICD-10: R06.5) were removed, after which 197 797 individuals remained in the control group. This did not reveal any new associations nor did it notably affect our estimates (supplementary figures S5 and S6, and supplementary table S4).

As an exploratory analysis we used MAGMA. We detected 25 significant associations ($p<2.54\times10^{-6}$) with various biological processes, which were driven by the same loci as the significant GWAS variants in *FTO* and *GAPVD1* (supplementary figure S7a). These may be potential target genes at these loci for the variants that associate with OSA and overall indicate that the genes at this region may be relevant for OSA. Similarly, the gene-based test for BMI-adjusted OSA revealed three further associated genes (supplementary figure S7b).

TABLE 2 Characterisation of five genome-wide significant obstructive sleep apnoea (OSA) loci in GRChb38

Chr.	Position	rsID	Ref.	Alt.	Nearest gene	Consequence	Fin. enr.	AF	AF cases	AF controls	INFO	OR (95% CI)	p-value	BMI-adjusted OR (95% CI)	BMI-adjusted p-value
16	53 765 595	rs9937053	G	A	*FTO*	Intron	0.97	0.43	0.45	0.43	0.999	1.11 (1.08–1.13)	4.3×10^{-16}	1.03 (1.00–1.06)	0.04
12	97 359 374	rs10507084	C	T	*RMST/NEDD1*	Intergenic	3.03	0.18	0.19	0.18	0.993	1.11 (1.08–1.15)	2.8×10^{-11}	1.12 (1.08–1.17)	9.7×10^{-10}
10	12 656 440	rs185932673	C	T	*CAMK1D*	Intron	0.55	0.0033	0.0051	0.0032	0.972	1.87 (1.50–2.33)	2.4×10^{-8}	1.75 (1.37–2.26)	9.3×10^{-6}
9	125 379 530	rs4837016	G	A	*GAPVD1*	Intergenic	1.12	0.47	0.45	0.47	0.995	0.93 (0.91–0.95)	1.5×10^{-8}	0.95 (0.92–0.97)	2.2×10^{-4}
2	136 234 237	rs10928560	C	T	*CXCR4*	Downstream	1.04	0.20	0.18	0.20	0.993	0.92 (0.89–0.94)	2.8×10^{-8}	0.93 (0.90–0.96)	8.5×10^{-5}

GRChb38: Genome Reference Consortium Human Genome build 38; Chr.: chromosome; Fin.enr.: Finnish enrichment (computed using Genome Aggregation Database (gnomAD) data comparing Finnish with other European populations in the gnomAD data); AF: allele frequency; INFO: imputation quality; BMI: body mass index; *FTO*: fat mass and obesity-associated protein; *RMST*: rhabdomyosarcoma 2 associated transcript; *NEDD1*: NEDD1 γ-tubulin ring complex targeting factor; *CAMK1D*: calcium/calmodulin-dependent protein kinase ID; *GAPVD1*: GTPase activating protein and VPS9 domains 1; *CXCR4*: C-X-C motif chemokine receptor 4. All effect sizes and AFs are reported in terms of the alternate allele. The finding of rs185932673 should be interpreted cautiously as the variant is rare in the Finnish population.

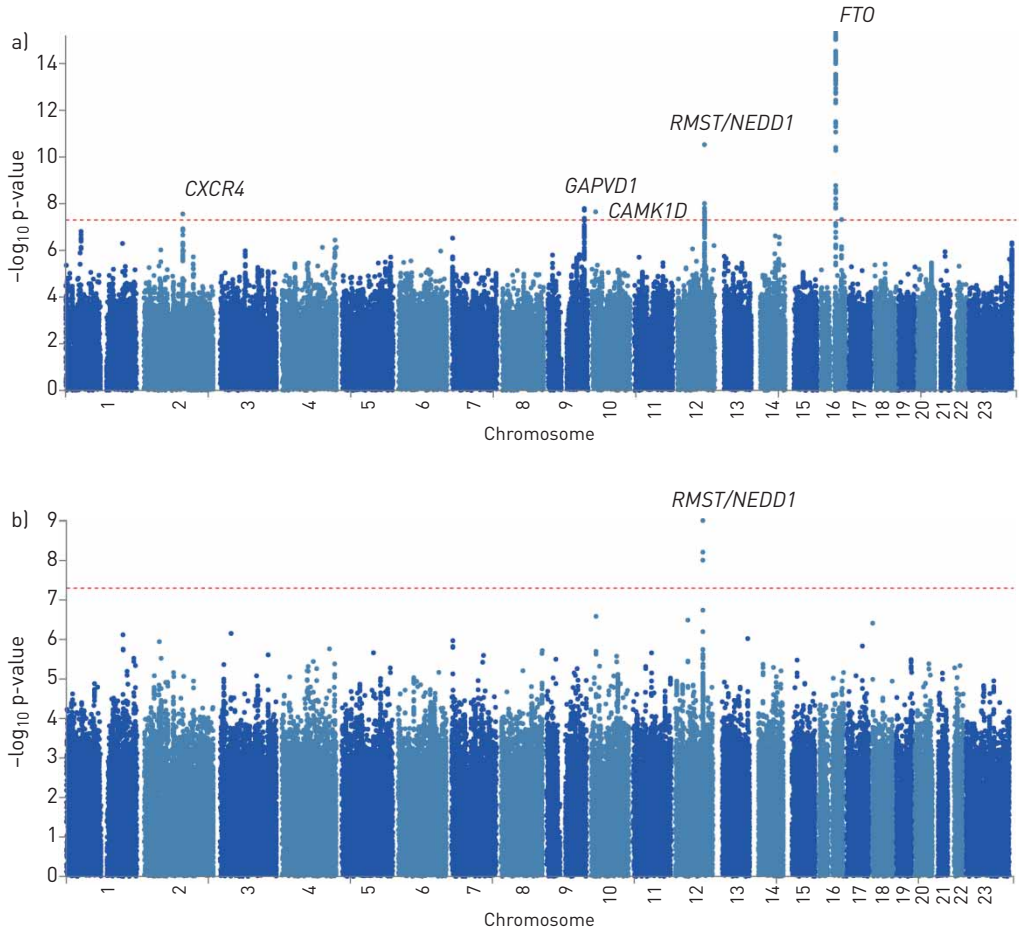

FIGURE 1 a) Manhattan plot for obstructive sleep apnoea (OSA) including 16 761 OSA cases and 201 194 controls. For each genetic variant, the *x*-axis shows the chromosomal position and the *y*-axis shows the $-\log_{10}$ p-value. The dashed horizontal line indicates the genome-wide significance threshold of $p=5\times10^{-8}$. Five genetic loci were identified at the genome-wide significance level: *CXCR4* (C-X-C motif chemokine receptor 4), *GAPVD1* (GTPase activating protein and VPS9 domains 1), *CAMK1D* (calcium/calmodulin-dependent protein kinase ID), *RMST/NEDD1* (rhabdomyosarcoma 2 associated transcript/NEDD1 γ-tubulin ring complex targeting factor) and *FTO* (fat mass and obesity-associated protein). b) Manhattan plot for OSA after body mass index adjustment including 12 759 OSA cases and 146 972 controls. For each genetic variant, the *x*-axis shows the chromosomal position and the *y*-axis shows the $-\log_{10}$ p-value. The dashed horizontal line indicates the genome-wide significance threshold of $p=5\times10^{-8}$. One genetic locus was identified at the genome-wide significance level: *RMST/NEDD1*.

We performed a phenome-wide association analysis (PheWAS) using FinnGen data and examined the associations between the lead SNPs and 2925 disease end-points. rs10507084 was specific for OSA also after adjusting for BMI, suggesting an independent role from cardiometabolic traits for the association between rs10507084 and OSA (figure 2a). While *FTO* was detected to be associated with OSA, it was also associated with a wide spectrum of cardiometabolic diagnoses, as shown previously [33, 38], and also with coffee consumption [41]. The strongest PheWAS associations were observed with OSA-related comorbidities, including obesity ($p=4.14\times10^{-41}$), T2D ($p=5.67\times10^{-28}$) and hypertension ($p=1.40\times10^{-10}$) (supplementary table S5). In addition, there was a strong correlation between rs10507084 and the use of antidepressants (OR 1.013 (95% CI 1.007–1.019); $p=4.4\times10^{-6}$) (figure 2b). This result remained significant after further adjusting for OSA (OR 1.011 (95% CI 1.005–1.017); $p=1.9\times10^{-4}$).

Genetic correlations and Mendelian randomisation connect OSA with cardiovascular outcomes and dysregulation of metabolism

To study the potential common genetic background of OSA and its known epidemiological correlates, we computed genetic correlations between OSA and its comorbidities using FinnGen summary statistics. The results showed strong genetic correlations between OSA and BMI ($r_g=0.72$ (95% CI 0.62–0.83); $p=3.49\times10^{-40}$) and between OSA and comorbidities: hypertension ($r_g=0.35$ (95% CI 0.23–0.48); $p=4.06\times10^{-8}$),

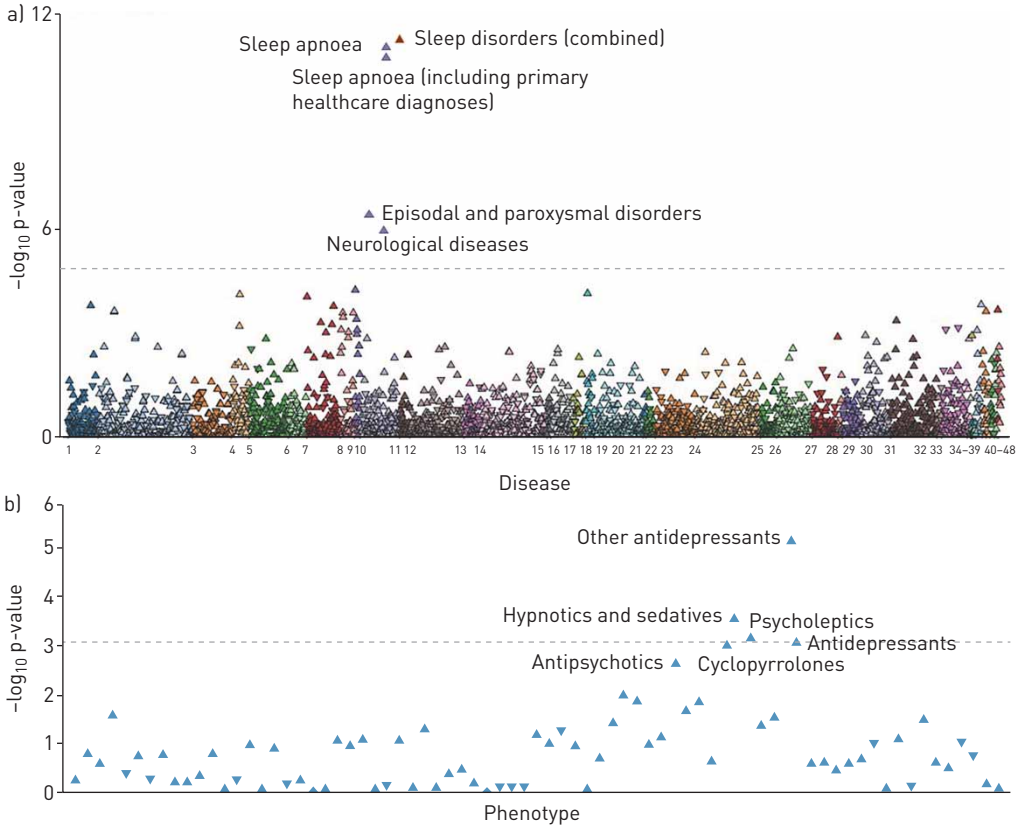

FIGURE 2 a) Phenome-wide association analysis (PheWAS) associations between rs10507084 and 2925 disease end-points after adjusting for body mass index. The Bonferroni corrected significance threshold was defined at p=0.05/2925=1.71×10^{-5}. Associated p-values are shown on the $-\log_{10}$ scale on the *y*-axis. Sleep apnoea represents a validated disease. Primary healthcare diagnoses have not been validated. Sleep disorders, episodal and paroxysmal disorders, and neurological diseases include sleep apnoea. The disease definition is shown along the horizontal axis (Roman numerals indicate International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) chapter numbers): 1) I Certain infectious and parasitic diseases, 2) II Neoplasms, from hospital discharges, 3) II Neoplasms, from cancer registry, 4) III Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism, 5) IV Endocrine, nutritional and metabolic diseases, 6) Diabetes end-points, 7) V Mental and behavioural disorders, 8) Psychiatric end-points, 9) Alcohol-related diseases, 10) VI Diseases of the nervous system, 11) Neurological end-points, 12) VII Diseases of the eye and adnexa, 13) VIII Diseases of the ear and mastoid process, 14) IX Diseases of the circulatory system, 15) Cardiometabolic end-points, 16) X Diseases of the respiratory system, 17) Asthma and related end-points, 18) Chronic obstructive pulmonary disease and related end-points, 19) Interstitial lung disease end-points, 20) XI Diseases of the digestive system, 21) Dental end-points, 22) Gastrointestinal end-points, 23) XII Diseases of the skin and subcutaneous tissue, 24) XIII Diseases of the musculoskeletal system and connective tissue, 25) Rheumatoid arthritis end-points, 26) XIV Diseases of the genitourinary system, 27) XV Pregnancy, childbirth and the puerperium, 28) XVI Certain conditions originating in the perinatal period, 29) XVII Congenital malformations, deformations and chromosomal abnormalities, 30) XVIII Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified, 31) XIX Injury, poisoning and certain other consequences of external causes, 32) XX External causes of morbidity and mortality, 33) XXI Factors influencing health status and contact with health services, 34) Drug purchase end-points, 35) Diseases marked as autoimmune origin, 36) Common end-point, 37) Demonstration end-points, 38) ICD-10 main chapters, 39) Operation end-points, 40) Other, not yet classified end-points, 41) Miscellaneous, not yet classified end-points, 42) Comorbidities of asthma, 43) Comorbidities of chronic obstructive pulmonary disease, 44) Comorbidities of diabetes, 45) Comorbidities of gastrointestinal end-points, 46) Comorbidities of interstitial lung disease end-points, 47) Comorbidities of neurological end-points, 48) Comorbidities of rheumatoid arthritis end-points. b) PheWAS analysis concerning drug purchases. The *x*-axis shows phenotypes based on Anatomical Therapeutic Chemical Classification System (ATC) drug codes and the *y*-axis shows the Bonferroni corrected significance threshold $-\log_{10}$ p-value, which was defined as 0.05/69=7.25×10^{-4}. The numbers of drug purchases were coded as continuous variables and inverse normalised to ensure normal distribution for analysis. Other antidepressant: ATC N06AX; hypnotics and sedatives: ATC N05C; psycholeptics: ATC N05; antidepressants: ATC N06A; cyclopyrrolones: ATC N05CF; antipsychotics: ATC N05A.

T2D (r_g=0.52 (95% CI 0.37–0.66); p=6.40×10^{-12}), CHD (r_g=0.38 (95% CI 0.17–0.58); p=3.84×10^{-4}), stroke (r_g=0.33 (95% CI 0.03–0.63); p=2.93×10^{-2}), depression (r_g=0.43 (95% CI 0.27–0.60); p=2.79×10^{-7}), hypothyroidism (r_g=0.40 (95% CI 0.27–0.54); p=7.07×10^{-9}), asthma (r_g=0.50 (95% CI 0.33–0.68);

p=1.53×10^{-8}) and IRD (r_g=0.34 (95% CI 0.09–0.58); p=6.97×10^{-3}). Furthermore, we observed high genetic correlations between OSA comorbidities. Since many OSA comorbidities are correlated with BMI, we calculated the genetic correlations after adjusting for BMI. This analysis showed somewhat lower estimates for genetic correlations between OSA and CHD (r_g=0.24 (95% CI 0.01–0.47); p=0.04), depression (r_g=0.33 (95% CI 0.17–0.50); p=1.1×10^{-3}), asthma (r_g=0.33 (95% CI 0.11–0.54); p=2.6×10^{-3}) and hypothyroidism (r_g=0.28 (95% CI 0.11–0.44); p=8.0×10^{-4}). Genetic correlations between OSA and BMI (r_g=0.08 (95% CI −0.05–0.22); p=0.22), hypertension (r_g=0.05 (95% CI −0.10–0.20); p=0.51), T2D (r_g=0.15 (95% CI −0.03–0.33); p=0.11), stroke (r_g=0.32 (95% CI −0.05–0.69); p=0.09) and IRD (r_g=0.27 (95% CI −0.01–0.54); p=5.7×10^{-2}) attenuated after adjusting for BMI (figure 3). We also estimated a strong genetic correlation between males and females (r_g=1.00 (95% CI 1.15–0.85); p=1.85×10^{-12}).

To estimate genetic correlations between FinnGen OSA summary statistics and other sleep traits, we used UKBB-derived summary statistics for sleep variables. We observed genetic correlation with snoring (r_g=0.81 (95% CI 0.69–0.93); p=1.24×10^{-38}) and sleep efficiency (r_g=−0.31 (95% CI −0.44–−0.17); p=9.80×10^{-6}), and this was reflected by higher genetic correlation with daytime sleepiness (r_g=0.44 (95% CI 0.33–0.54); p=1.27×10^{-15}) [16, 28, 30]. These associations also remained significant after adjusting for BMI (r_g=0.68 (95% CI 0.55–0.81); p=2.93×10^{-26}, r_g=−0.19 (95% CI −0.36–−0.03); p=0.02 and r_g=0.42 (95% CI 0.29–0.55); p=1.06×10^{-10}, respectively). We did not find significant genetic correlations between OSA and sleep duration or chronotype (table 3) [29].

To investigate the biological mechanisms behind OSA, we also examined tissue enrichment of association signals using partitioned heritability analysis using LDSC, an approach that combines data from the ENCODE and GTEx resources [31, 32] to FinnGen OSA summary statistics. Concordantly with the association of BMI and cardiometabolic traits, we observed the strongest associations with cardiovascular tissues and connective and bone tissues (p<0.05). Furthermore, enrichments with BMI-adjusted OSA implicated the central nervous system as the strongest associating single tissue (p<0.05) when a nominal α-level of 0.05 is shown (supplementary figure S8).

To test if there is a causal relationship between OSA and its comorbidities, we performed analysis of PRS followed by formal Mendelian randomisation analysis using FinnGen OSA summary statistics and independent BMI SNPs [33]. The BMI PRS showed a strong association with OSA risk (table 4) and the individuals in the highest BMI PRS quintile had 1.98 (95% CI 1.88–2.09)-fold increased (p=3.38×10^{-140})

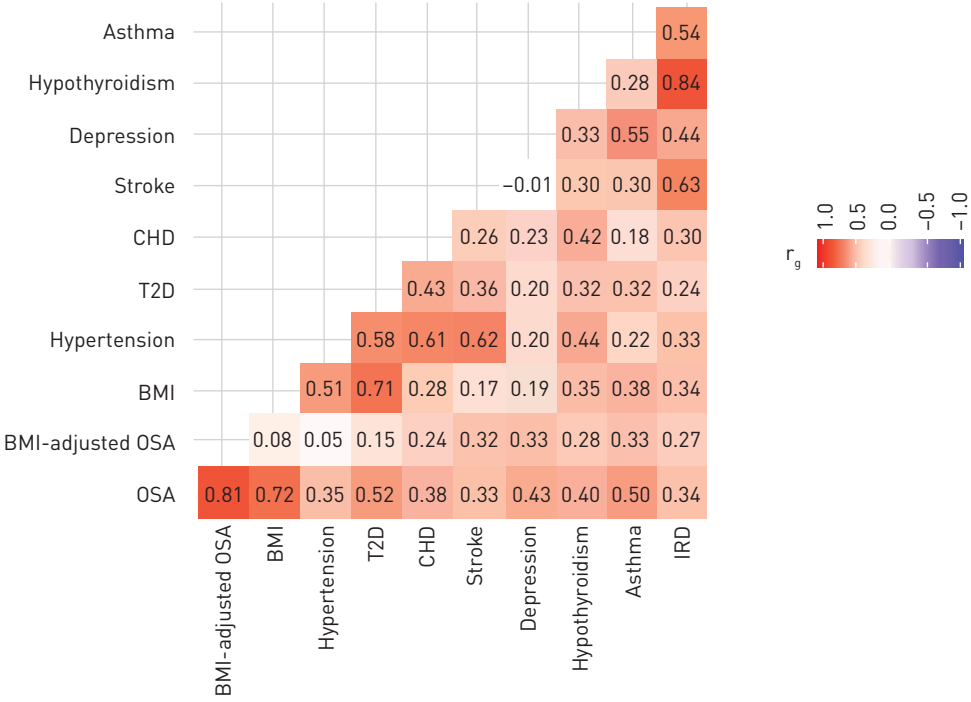

FIGURE 3 Genetic correlations (r_g) between obstructive sleep apnoea (OSA), body mass index (BMI) and previously known comorbidities using linkage disequilibrium score regression. CHD: coronary heart disease; T2D: type 2 diabetes; IRD: inflammatory rheumatic disease. The colour scale represents the strength of the correlation. Correlations between OSA and other traits have been calculated with and without adjusting for BMI.

TABLE 3 Genetic correlations between obstructive sleep apnoea (OSA) and other sleep traits

	Snoring	Sleepiness	Sleep duration	Chronotype	Sleep efficiency
OSA					
r_g (95% CI)	0.81 (0.69–0.93)	0.44 (0.33–0.54)	0.01 (−0.09–0.10)	-5.0×10^{-4} (−0.08–0.08)	−0.31 (−0.44–−0.17)
p-value	1.24×10^{-38}	1.27×10^{-15}	0.84	0.99	9.80×10^{-6}
BMI-adjusted OSA					
r_g (95% CI)	0.68 (0.55–0.81)[#]	0.42 (0.29–0.55)	0.08 (−0.03–0.19)	−0.06 (−0.15–0.03)	−0.19 (−0.36–−0.03)
p-value	2.93×10^{-26}	1.06×10^{-10}	0.14	0.18	0.02

Summary statistics for sleep traits that were used to calculate the genetic correlations were obtained in previous genome-wide association studies (GWASs) from the UK Biobank. BMI: body mass index. [#]: GWAS for snoring was also adjusted for BMI.

OSA risk after adjustment for age, sex and the 10 first PCs. Similarly, this association was further accentuated in formal Mendelian randomisation. We used 64 independent BMI SNPs [33] as instrumental variables to predict OSA. In line with epidemiological observations and genetic correlation, we discovered a strong causal predictive effect from BMI to OSA (inverse variance weighted: β=0.67; $p=8.32\times10^{-16}$) (figure 4 and supplementary table S6).

Replication

For each lead variant associated with OSA, we examined the estimates from the additional, comparable cohorts, *i.e.* UKBB, EGCUT and ANDIS. The results were combined using inverse variance weighted fixed-effect meta-analysis. These additional independent datasets support the role of *FTO* and *GAPVD1* loci in OSA ($p<0.05$) (supplementary table S7a).

In addition, we calculated the PRS using the lead variants from our study and UKBB's individual-level data to predict OSA. The OSA PRS showed an association with OSA risk and the individuals in the highest OSA PRS quintile had a modest 1.24 (95% CI 1.15–1.33)-fold increased ($p=6.89\times10^{-9}$) OSA risk compared with the lowest quintile after adjusting for birth year, sex and the 10 first PCs. Furthermore, the association was adjusted for BMI in addition to the aforementioned covariates, showing a somewhat lower but significant estimate (OR 1.11 (95% CI 1.03–1.20); $p=4.70\times10^{-3}$) (supplementary table S8).

Discussion

In this study, using biobank data of over 217 000 individuals, we show that OSA risk has a strong genetic component and identify five genetic loci that are associated with the risk for OSA. Our results show high genetic correlations between OSA and cardiometabolic diseases and risk factors, with the strongest connections between OSA and BMI, hypertension, T2D and CHD, which are in line with previous epidemiological and clinical observations. These genetic correlations tracked with phenotypic correlations and comorbidities for OSA. In addition, both our association findings and the Mendelian randomisation results support the causal role of obesity in OSA.

These results allow us to draw several conclusions. First, genetic variation plays an important role in the development of OSA. This is supported by both the SNP heritability estimates and the associated loci.

Second, our results show that obesity plays a central causal role in OSA risk. This is supported by high genetic correlations between OSA and BMI. We found that four out of five associated loci were mediated through their associations with BMI. These findings are in line with the finding that weight loss is an important contributor to lowering AHI and the severity of OSA [42, 43].

TABLE 4 Estimated effect coefficients for body mass index (BMI) polygenic risk score (PRS) as a predictor of obstructive sleep apnoea (OSA)

BMI PRS quintile	OR (95% CI)	p-value
1 (lowest)		
2	1.29 (1.22–1.36)	3.49×10^{-19}
3	1.45 (1.37–1.53)	5.61×10^{-40}
4	1.61 (1.53–1.70)	7.93×10^{-67}
5 (highest)	1.98 (1.88–2.09)	3.38×10^{-140}

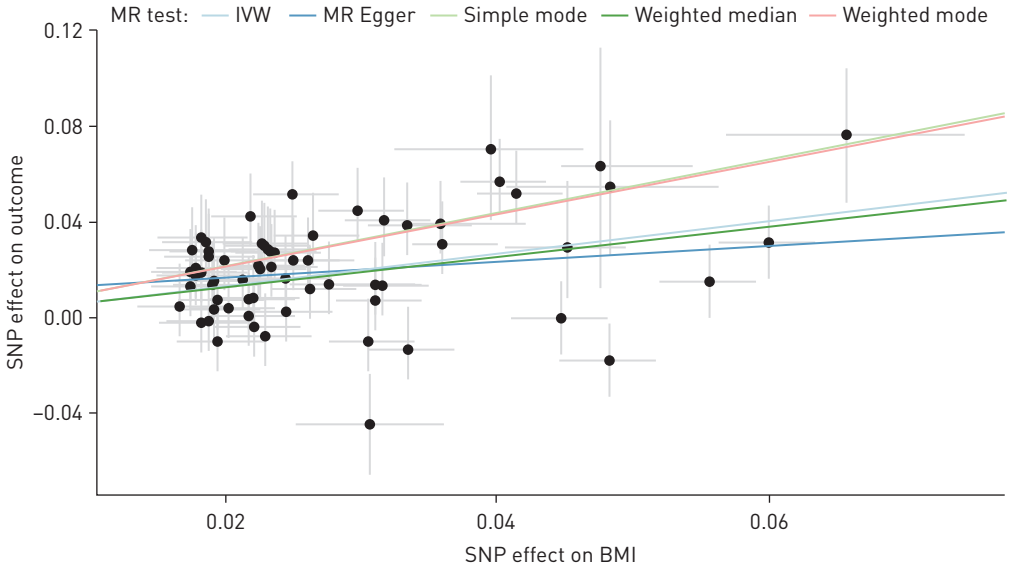

FIGURE 4 Formal Mendelian randomisation (MR) suggesting a strong causal relationship between body mass index (BMI) and obstructive sleep apnoea (OSA) where BMI predicts OSA as an outcome. SNP: single nucleotide polymorphism; IVW: inverse variance weighted.

Third, we also identified an association near *RMST*/*NEDD1* that was specific for OSA independent of BMI. The lead SNP was associated with antidepressant purchases, which connects this locus with regulation of sleep and mood. The finding may also reflect the earlier observation that depression is prevalent among patients with OSA [8].

Fourth, a strong genetic correlation was observed between OSA and sleep traits, especially sleepiness and sleep efficiency. These findings highlight the pathological effects of OSA on sleep. As OSA is manageable with continuous positive airway pressure (CPAP) or an oral appliance, these findings support OSA treatment as it may reduce sleepiness and increase sleep efficiancy.

Our study does have some limitations. First, registry-based ascertainment through hospitalisation may miss nonhospitalised cases (false negatives) and treatment information such as CPAP compliance or oral sleep apnoea appliance usage. However, to the best of our knowledge, this is the largest number of cases combined for a GWAS. Second, due to the relatively small number of cases in the replication datasets, our statistical power was limited in the replication analysis. The finding of rs185932673 should be interpreted cautiously as the variant is rare in the Finnish population and the association was not replicated in the other study samples.

Here we present associations between five genetic loci and OSA. Two of these were replicated in independent cohorts. Our findings highlight the causal links between obesity and OSA, but also provide evidence for non-BMI-dependent genetic effects. In addition to BMI, we show that genetic effects that modify the risk of cardiometabolic diseases, depression, hypothyroidism, asthma and IRD are also correlated with genetic effects for OSA, showing that the observed comorbidities between OSA and these diseases may have a joint genetic basis. Our results support that OSA is a heterogenic disease with several distinct comorbidities, which would be beneficial to consider when treating patients with OSA.

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